

Advances in the treatment of multiple myeloma in patients with chromosome 13 abnormalities

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This column is based on the format of an Elsevier textbook entitled *Hematology and Oncology Pearls*, by Dr. Danso and Ethan Basch, which challenges readers to formulate a diagnosis and treatment plan.

The landscape of therapeutic options for multiple myeloma is changing rapidly. The use of newer melphalan (Alkeran)-based combinations¹⁻⁹ has shown improvements in response rate, time to disease progression, and survival in older adults with newly diagnosed multiple myeloma. The objective of this article is to review some of these recent advances.

Case presentation

A 69-year-old man presented to the emergency room after a fall. X-ray examination revealed a pathologic fracture to the neck of the left femur and multiple lytic lesions in the calvaria, long bones, and ribs. Laboratory findings included a serum calcium level of 11.5 mg/dL, albumin level of 3.2 g/dL, creatinine concentration of 2.5 mg/dL, hemoglobin level of 11 g/dL, and a β_2 -microglobulin level of 3.5 mg/L. A bone marrow biopsy demonstrated 90% cellularity, with 50% plasma cells. Cytogenetic analysis revealed a 13q14 deletion.

Question: What is the most likely diagnosis in this patient?

Answer: Multiple myeloma.

Treatment options

Patients with newly diagnosed multiple myeloma who are symptomatic are candidates for chemotherapy-based interventions. Therapeutic options also include

high-dose chemotherapy with autologous stem-cell transplantation (ASCT).¹⁰ Clinical criteria that can help decide whether stem-cell rescue is warranted include the patient's age, performance status, and existing comorbidities.¹⁰

Patients with multiple myeloma can be risk-stratified on the basis of the International Staging System (Table 1), their age, and the presence of cytogenetic abnormalities detected by routine karyotyping or fluorescence in situ hybridization.^{11,12} Chromosome 13 abnormalities are more strongly associated with unfavorable outcomes after both conventional chemotherapy and ASCT.¹³⁻¹⁸

The presence of various cytogenetic abnormalities may influence the choice of initial chemotherapy in the future. Bortezomib (Velcade) therapy in patients with a 13q deletion can produce durable response rates, suggesting that this agent is able to overcome the adverse affects of del(13) abnormalities.¹⁹⁻²¹

Question: What is the best option for induction therapy in this elderly patient?

Answer: Currently, the best choice appears to be bortezomib-based combination therapy, given the presence of a 13q abnormality.

Induction therapy

Melphalan and prednisone (MP), as well as pulses of dexamethasone, have been the standard of care for older adults with multiple myeloma who are not eligible for ASCT. Several studies with newer combinations of these and other agents in multiple myeloma have been reported.

Melphalan and dexamethasone

The Intergroupe Francophone du Myélome (IFM) randomized 488 previously untreated patients who were 65–75 years of age to receive MP, melphalan and dexamethasone (MD), dexamethasone alone, or dexamethasone and interferon alfa. Although none of these regimens in-

TABLE 1
International Staging System for multiple myeloma

Stage	Criteria	Median overall survival, months
I	Serum β_2 -microglobulin level < 3.5 mg/L and serum albumin \geq 3.5 g/dL	62
II	Neither stage I nor III*	44
III	Serum β_2 -microglobulin level \geq 5.5 mg/L	29

* There are two categories for stage II: a serum β_2 -microglobulin level < 3.5 mg/L with a serum albumin level < 3.5 g/dL or a serum β_2 -microglobulin level \geq 3.5 mg/L but < 5.5 mg/L, irrespective of the serum albumin level.

Adapted from Greipp et al¹²

duced a significant number of complete responses, patients receiving MD had a 70% overall response rate, defined as achieving at least a partial response, which was significantly higher than that seen with any of the other three regimens.²² However, the MD regimen was associated with a greater risk of severe toxicity, most notably severe pyogenic infections (including pulmonary infections and septicemia), in agreement with the results of previous studies of this regimen. Moreover, the higher response rate observed with MD did not translate into either a significantly superior median time to disease progression or median overall survival.

Melphalan, prednisone, and thalidomide

The combination of MP plus thalidomide (Thalomid; MPT) has been tested in two phase III trials against the standard MP regimen. Palumbo et al⁴ reported a randomized phase III trial comparing MP with MPT as initial therapy in multiple myeloma patients aged 60–85 years. Patients receiving MPT had a higher overall response rate (76%) compared with those randomized to treatment with MP (48%), and the quality of the responses was better as well (with more complete, near-complete, and “very good” partial responses). Long-term follow-up showed that 42 of 129 patients (33%) treated with MPT suffered disease progression, relapse, or death, compared with 62 of 126 (49%) of those who were not treated with thalidomide. This difference translated into a 2-year event-free survival rate of 54% in the MPT arm versus 27% in the MP arm ($P = 0.0006$). At 3 years, the overall survival rate was 80% for those patients receiving MPT versus 64% for those treated with MP alone ($P = 0.19$). However, MPT was associated with a significantly increased risk of grade 3 or 4 thromboembolic

complications, neurologic toxicities, infectious events, and gastrointestinal problems, compared with MP. As a result of the thromboembolic complications, prophylaxis with low-molecular-weight heparin (enoxaparin [Lovenox]) was instituted, which reduced the rate of thromboembolism from 20% to 3%.

A randomized phase III trial comparing MP and MPT has also been performed by the IFM.⁵ This study incorporated a third arm with standard induction chemotherapy followed by mobilization and an intermediate-dose (100 mg/m²) of melphalan supported by stem-cell rescue. As was the case in the Italian study of MPT reported by Palumbo et al, investigators in the French trial found a higher overall response rate for MPT compared with MP, and a better response quality as well, with more complete and very good partial responses. Importantly, both progression-free and overall survival rates were superior among patients receiving MPT compared with those treated with MP ($P < 0.001$ and $P = 0.001$, respectively) or 100 mg/m² of melphalan alone ($P = 0.001$ and $P = 0.004$, respectively).

Together, these two randomized phase III studies strongly support the use of MPT as the current standard of care for older patients who are newly diagnosed with multiple myeloma and require chemotherapy.

Melphalan, prednisone, and bortezomib

Bortezomib was incorporated into the MP regimen (VMP) by the Grupo Español de Multiple Myeloma in a phase I/II trial of 60 elderly patients (≥ 65 years of age) with previously untreated multiple myeloma.⁸ The overall response rate was 89%, including 32% of patients with a complete response and an additional 11% with a near-complete response. Event-free and overall survival rates at 16 months of follow-up were 83% and 90%, respective-

ly, which compared favorably with the group's historic controls for MP alone of 51% and 62%. Importantly, all 13 patients with a chromosome 13 deletion achieved at least a partial response, including 54% with either a complete or near-complete response. These encouraging results formed the basis of an ongoing phase III trial comparing MP with VMP.

Melphalan, prednisone, and lenalidomide

Although MPT provides a survival advantage compared with MP,^{4,5} its use, as discussed above, is associated with a higher risk of adverse events, providing the impetus for substitution of lenalidomide (Revlimid) for thalidomide in the MPT regimen. Results from a phase I/II study of MP with lenalidomide (R-MP) have recently been presented.⁷ The overall response rate in this study for all four patient cohorts after a median of 7 cycles of therapy was 85%, including 17% of patients who achieved a complete response and 24% who achieved a near-complete response. Event-free survival at 16 months of follow-up in 53 patients was 87% and compared favorably with the 71% rate seen at 18 months for historic controls treated with MPT.

Interim results of a phase III study comparing MP with combination thalidomide-dexamethasone therapy showed that the latter regimen seems to induce a higher overall and complete response rate.²³ However, more patients receiving thalidomide and dexamethasone suffered progressive disease; additional follow-up is needed to determine which regimen is superior. Meanwhile, data from two additional single-arm studies of thalidomide and dexamethasone^{24,25} have shown a briefer median time to disease progression and overall survival than has been reported with MPT, indicating that a thalidomide/dexa-

methasone regimen may not be the optimal choice for patients who cannot undergo ASCT.²⁶

Role of transplantation

The benefit of ASCT in older patients with multiple myeloma has not been formally established in randomized trials. The median age in most transplant studies is ~ 55 years.^{27–29} However, there are studies to report that ASCT is safe in patients over the age of 70.^{30,31} A randomized study from the French group Myeloma-Autogreffe (MAG) in patients aged 55–65 years with a 10-year follow-up suggests that, despite higher response rates and event-free survival rates, ASCT offers no survival benefit over chemotherapy.³² In this study, however, 22% of patients in the chemotherapy group underwent ASCT at relapse, contributing to the similarity in overall survival. The results of the IFM trial comparing MP and MPT with ASCT provide further evidence that MPT is able to improve complete response rates and overall survival when compared with stem-cell transplantation.⁵ In addition, the negative impact of harboring a del(13) chromosome abnormality is not overcome by either autologous or allogeneic transplant strategies. The median survival after a single ASCT in patients with a del(13) abnormality ranges from 24 to 27 months, compared with > 60 months in patients without a del(13) abnormality.^{13,15–18}

Clinical pearls

1. Patients with multiple myeloma who are discovered to have chromosome 13 abnormalities are more likely to have unfavorable outcomes after both conventional chemotherapy and ASCT than patients without chromosome 13 abnormalities.

2. For symptomatic elderly patients with multiple myeloma, induction therapy with MPT is most likely the best option. If a deleted

chromosome 13 is noted by cytogenetic analysis, a bortezomib-based combination would be preferred as initial therapy.

3. The role of ASCT in older patients with multiple myeloma is still unclear, particularly in the presence of a cytogenetic abnormality.

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